DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

For M3786n

19900 MacArthur Blvd., Ste 300
Irvine, California 92612-2445
Telephone (949) 798-7600

WARNING LETTER

MAR 2 2 2000

CERTIFIED MAIL – RETURN RECEIPT REQUESTED

W/L 45-00

Jack Y. Zhang, Ph. D.
President and CEO
International Medication Systems, Limited
1886 Santa Anita Avenue
South El Monte, CA 91733

Dear Dr. Zhang:

During an inspection of your manufacturing facility located 1886 Santa Anita Avenue, South El Monte, CA, conducted January 13th through 28th and February 9th, 2000, our FDA investigators documented deviations from the Current Good Manufacturing Practices (cGMPs) for Finished Pharmaceuticals (Title 21, Code of Federal Regulations, (CFR) §211). Those deviations cause all drug products manufactured at your facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The violations from 21 CFR §211 include:

1. Failure to establish production and process control procedures designed to assure your drug products have the required identity, strength, quality and purity [21 CFR §211.100(a)]. For example, you have failed to qualify or validate the room used to incubate samples for real time stability testing and media fill vial incubation and the addition of a N_2 headspace to vials containing O_2 sensitive products, among other things.

2. Failure to follow and appropriately document written production and process control procedures [21 CFR §211.100(b)]. For example, you did not perform annual re-qualification of stability incubators or investigate non-conforming product as required by Standard Operating Procedures that you established, among other things.

3. Failure to establish valid in process specifications based from previous acceptable process average and process variability estimates [§211.110(b)]. For example, bulk bioburden specifications were increased without justification; the change was not supported by historical data.

4. Failure to establish and document the accuracy, sensitivity and reproducibility of test methods employed [§211.165(e)]. For example, the method used to determine the microbiological quality of Water for Injection does not reflect actual sample values and there are no or vague inspection parameters/specifications for particulate matter in your [redacted] product.

5. Failure to follow a written testing program designed to assess the stability characteristics of drug products [§211.166(a)(1)]. For example, additional Phytonadione samples from several different lots were pulled from stability sample inventory without justification; there is no documentation of the test results for these additional samples.

6. Failure to follow sampling plans, test procedures or other laboratory control procedures [§211.160(a)]. For example, there is no justification for pulling additional samples for finished product testing nor is their documentation of the test results for [redacted].

7. Failure to ensure that complete data derived from all tests necessary to ensure compliance with established specifications are maintained [21 CFR §211.194(a)]. For example, data is recorded on uncontrolled worksheets in the performance of LAL testing. The use of the uncontrolled worksheet allows data to be discarded without your knowledge.

8. Failure to investigate evidence of reserve sample deterioration [211 CFR §211.170(b)]. For example, particulate matter was observed in several lots of [redacted] reserve samples during your annual product review; there is no documented evidence that the particulate matter was present during manufacturing or at the time of product release.

9. Failure to document laboratory control procedures at the time of performance [§211.160(a)]. For example, test data such as temperature of heat block incubator, sample identification number, and order of sample loading into the heat block incubator was not recorded during the actual performance of Limulus Amebocyte Lysate (LAL) testing for Bacterial Endotoxins.

10. Failure to retain a reserve sample that is at least twice the quantity necessary for all required tests (except pyrogen and sterility) [21 CFR §211.170(b)].

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your South El Monte, CA facility. We acknowledge the immediate corrective actions you took during the inspection and committed to in your response to the FDA-483 you submitted to the district office. However, it is your continuing responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. You should take prompt action to correct these deviations and prevent their recurrence. Failure to promptly correct these deviations may result in

regulatory action without further notice. Possible actions include seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, New Drug Applications, Abbreviated New Drug Applications or export approval requests may not be approved until the above violations are corrected.

In addition, we offer the following comments:

During the inspection, the manufacture of medical devices at your facility was also covered. Deficiencies involving management controls, design controls, production and process controls and nonconforming product were cited on the FDA-483. This letter is intended to address the deficiencies associated with your drug manufacturing processes and adherence to drug GMPs. The observations relating to device manufacturing and Quality Systems Regulations (QSR) are currently under review in the district and may be addressed at a later date.

You should notify this office in writing within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed.

Your written response should be directed to the Food and Drug Administration, Attention:

Thomas L. Sawyer
Director, Compliance Branch
Food and Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

Sincerely,

Acting District Director

cc: California Department of Health Services, Food & Drug Branch
601 N. 7th Street
Sacramento, California 94234-7320
Attn: Stuart Richardson, Jr., Chief